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Immunotherapy and other systemic therapies for cutaneous SCC

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ABSTRACT

Contrary to the impression that non-melanoma skin cancer is a banal and relatively trivial malignancy it causes about 1% of all cancer deaths. Cutaneous Squamous Cell carcinoma (CuSCC) make up a significant part of these deaths either from incurable loco-regional disease or metastatic disease. As is typical of the disease itself, these patients are often of advanced age, but the immunocompromised from organ transplantation or haematological malignancy are important populations.

Systemic therapies have a long history in palliative therapy for CuSCC, but not a particularly extensively studied one. Cytotoxic chemotherapy is active with response rates derived from multiple small studies of 17–85%; as is often the case in solid tumour oncology responses are rarely durable. The Epidermal Growth Factor Receptor has been targeted with both small molecular inhibitors and monoclonal antibodies. Disease control rates of the order of 50–70% were seen but again durability remains an issue. Immunotherapy using interferon with retinoids also showed significant response rates in very small trials.

The high rates of mutation seen in CuSCC and relationship with immunosuppression suggested that checkpoint inhibitors might be active. Checkpoint inhibition immunotherapy with PD-1 antibodies like cemiplimab have demonstrated response rates of the order of 40% and durability is encouraging: response duration was over a year in 75% of responders in the initial trial. We review the latest data with current immunotherapy drugs and consider the future directions such therapy may take us as well as the role of these therapies in special populations.

Introduction

A proportion of patients with cutaneous SCC (CuSCC) have disease that is no longer amenable to curative therapy because there is distant metastasis or locoregional modalities have failed or have been rejected. In the locoregional case this may be disease that is deeply invasive or disease that has recurred after prior local treatments such as surgery or radiotherapy. For some of these patients further surgery or radiotherapy cannot be used (due to tumour or patient factors) or is not likely to result in cure. Unresectable, locally advanced cuSCC can be lethal without ever developing distant metastatic disease [1]. Mortality from non-melanoma skin cancers (of which cuSCC likely make up a large part) is approximately 1% of all cancer deaths in Australia and is increasing [2]. In the US it is estimated around 2000 people die from SCC and BCC combined each year [3]. Thus, patients with metastatic SCC and some with unresectable locally advanced disease are candidates for systemic therapy.

Systemic therapy before checkpoint inhibitors (CPI)

Prior to the advent of modern checkpoint inhibitor (CPI) immunotherapy (see Oiseith et al. [4] for an historical review of cancer immunotherapies), treatment options included conventional chemotherapy, Epidermal Growth Factor Receptor (EGFR) targeted therapy and interferon. The literature base for systemic treatments of advanced cuSCC consists of small case series and phase II studies.

Chemotherapy

Whilst it is derived from small studies with varying eligibility criteria, conventional chemotherapy has useful palliative activity in cuSCC with response rates ranging from as low as 17% for some metastatic patients up to 86% for locally advanced patients [5]. Reports include the use of multiagent chemotherapy including platinum compounds, 5-Fluorouracil and derivatives, taxanes, as well as other drugs such as doxorubicin and bleomycin although these are not widely used currently [6–8]. As advanced cuSCC often occurs in elderly patients who

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may have significant co-morbidities, reduced functional and physiological reserves and limited social supports the risk of toxicity from chemotherapy is a major consideration. Cartei et al. [9] used an oral 5-Fluorouracil analogue in a cohort of 14 elderly patients with minimal toxicity; 9 patients had either a response or stable disease. Although occasional patients were reported to be disease free for up to 2 years after chemotherapy [7,8] in the majority of cases responses are not durable. Disease regrowth is then typically resistant to re-treatment with further chemotherapy. As in other metastatic or incurable solid malignancies this is a major disappointment with conventional chemotherapy.

The epidermal growth factor receptor (EGFR)

Targeting the EGFR receptor has been another strategy in systemic therapy. EGFR is frequently expressed on cuSCC cells [10]. EGFR can be targeted with small molecule tyrosine kinase inhibitors (also used widely in non-small cell lung cancer) and by antibodies (used in head and neck mucosal SCC and colorectal cancer). We will review the literature more extensively than with chemotherapy because it is newer and trial patients are more reflective of current practice than those treated in the chemotherapy trials, many of which were performed in the 1980s or earlier [5].

Maubec et al. [11] treated 36 patients with cetuximab with 2 complete and 8 partial responses for a 69% rate of disease control at 6 weeks (the trial's primary endpoint). Of note these patients were fairly typical for the real world with a median age of 79. However responses were not durable: median progression free survival (PFS) was about 4 months, median overall survival (OS) was about 9 months and 3 serious adverse events were noted. Foote et al. [12] used the humanised anti-EGFR antibody Panitumumab and treated 16 patients, of whom 14 had previous radiotherapy and 7 previous chemotherapy. The median age was 69. Two complete and 3 partial responses were seen as well as 6 patients with stable disease. The median duration of response was 6 months and acceptable toxicity was noted.

The EGFR inhibiting small molecule drugs erlotinib and gefitinib have also been considered for use in cuSCC. William et al. [13] used gefitinib 250 mg daily in 40 patients with unresectable or metastatic cuSCC and showed 6 partial responses among 27 patients with locally advanced disease but no objective responses in 8 patients with metastatic disease. A further 13 patients overall had stable disease at 8 weeks for a clinical benefit rate of 51% in the 37 evaluable patients. Median PFS was 3.8 months and median OS was 12.9 months. Gold et al. [14] reported a 10% response rate and 72% disease control rate with erlotinib 150 mg daily for unresectable cuSCC in a trial recruiting 39 patients of whom 29 were evaluable. Median PFS was 4.7 months and median OS was 13 months. Gefitinib has been studied in the neoadjuvant setting in 22 patients with complete responses in 18% and partial responses in 27% [15].

Overall EGFR targeted agents appear to have some activity in cuSCC and are generally reasonably tolerated; protracted therapy is possible as cumulative toxicities are usually manageable. There is a rational basis to consider potentially combining these agents with CPI, perhaps more particularly with the anti-EGFR antibodies where some of their activity is thought to be immunological, related to their ability to trigger Antibody Dependent Cell cytoxicity (ADCC) [16,17].

"Old" immunotherapy

Interferons were one of the earliest classes of immune acting anticancer agents discovered and tested in various cancers over three decades ago. Interferon alpha 2a (3×10^6 units daily) combined with the differentiating agent 13 cis-retinoic acid (13cRA) (1 mg/kg po daily) was used to treat 28 pts with a mix of locally advanced, regional and metastatic cuSCC. Significant response rates were observed, particularly in locally advanced disease with 6 complete and 7 partial responses out of 13 patients; there were 4 PR in 6 regional and 1 PR and 1 CR in 8 metastatic cases. Toxicity was typical of interferon with grade 3 fatigue in almost all and severe flu like symptoms in a quarter [18]. These agents were also combined with chemotherapy in attempt to enhance efficacy. Cisplatin (20 mg/m^2 weekly) + IFN (5×10^6 units $\times$ 3/week sc) + 13cRA (5×10^6 units $\times$ 3/week sc) was used to treat 39 patients with locally advanced and metastatic cuSCC. The response rate was 67% in the locally advanced patients but only 17% in the metastatic group. A median survival of 14.6 months and 2-year overall survival of 32% were reported. Toxicity in this trial included neutropenic sepsis in 6% and moderate to severe neutropenia in 38% [19].

"New" immunotherapy

The development of understanding of immune checkpoints [20] and the ability to manipulate this fundamental aspect of immune biology has lead to an explosion of treatment in diseases previously considered "hard to treat" such as melanoma with profound and durable responses [21].

The essence of this understanding is that there is a mechanism to prevent untrammelled activity of the adaptive immune response. This consists of a number of so-called checkpoints that need to be passed in order for an immune response to proceed. Simply put, in the context of an immune stimulus, a further set of signals must be present for the T-cell to continue toward activation. This is depicted in Fig. 1. There is a network of such bottlenecks that serve to regulate the immune response and prevent excessive activity toward self-antigens [20]; this network continues to be unravelled [22–24]. In 2019 two of the checkpoints, those modulated by CTLA-4 and Programmed Cell Death-1 (PD-1)/Programmed Cell Death Ligand-1 (PD-L1) have inhibitors that are in routine clinical use [22].

Rationale for CPI in CuSCC

Avoidance or abrogation of immune surveillance appears a significant event in the development of cuSCC. Sun exposed patients with iatrogenic immune suppression following solid organ transplants have a 65–250 fold increase in the risk cuSCC [25], their outcomes are worse than immunocompetent patients [26] even when controlling for multiplicity of tumours; cessation of immunosuppression can result in dramatic decreases in new CuSCC [27], and less immunosuppression results in lower rates of malignancy [28]. Incidence of cuSCC overall increases with age consistent with age related immune senescence [29]. Furthermore, response to CPI treatment across multiple cancers has been shown to have some correlation with tumour mutation burden as determined by tumour genome sequencing. cuSCC has been reported to have high average tumour mutation burden, generally higher than most other cancers including melanoma [30] and is eclipsed only by cutaneous BCC [31]. The high tumour mutation burden presumably reflects the extensive, cumulative UV induced mutation load driving malignant transformation in keratinocytes. Collectively, these features suggested that cuSCC may well be sensitive to CPI therapy.

Clinical trial results and other data for CPI

The largest peer reviewed evidence for use of CPI in cuSCC comes from studies of Cemiplimab. Cemiplimab is a humanised IgG4 antibody directed against the Programmed Cell Death-1 (PD-1) receptor, resulting in blockade of signalling between PD-1 and its ligands PD-L1 and PD-L2. We will discuss this in some detail, as this appears the start of a new and highly promising approach to therapy.

The phase I study was expanded after a clinically significant response was seen in a patient with advanced CuSCC and then a phase II trial was initiated (NCT02383212 and NCT02760498). This experience was reported in 2018 [32]. All patients were treated with 3 mg/kg

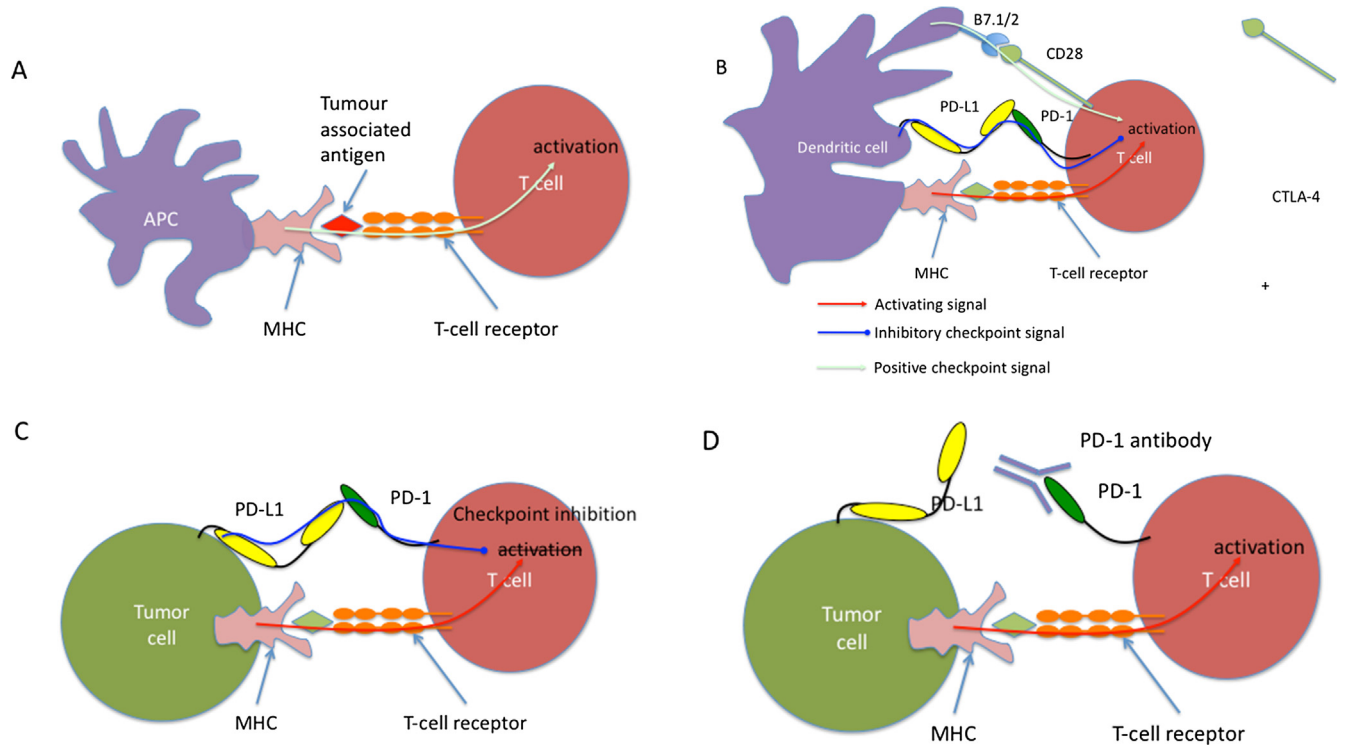

Fig. 1. . Cartoon depiction of T-cell activation and the function of checkpoints. (A) A T-cell is activated simply without any restraint. Any stimulus including self-antigens will result in activation, an obviously undesirable situation. (B) To prevent any activating signal from causing activation of system of inhibitory and stimulatory co-signals is present. Here the PD-1/PD-L1 system is depicted as a negative signal and the B7.1/2/CD28 system is used to show a stimulatory positive signal. The balance of these and other signals results in overall activation of the T-cell. (C) A tumour cell can utilize this to escape immunological surveillance by expressing PD-L1 on the surface and thus triggering the inhibitory checkpoint signal and preventing T-cell activation. (D) The presence of a PD-1 antibody prevents the inhibitory signal from impairing activation of the T-cell in response to the immune stimulus. Abbreviations: MCH major histocompatibility class, PD-1 programmed death-1, PD-L1 programmed death ligand-1.

Table 1
Clinical population and response rates to cemiplimab in the initial trial [32].

	Phase I	Phase II
Number	26	59
Median age (range)	73 (55–88)	71 (38–93)
Head and neck primary site	69%	64%
Prior radiotherapy	77%	85%
Prior systemic therapy	69%	56%
Locally advanced only	38%	0%
Response rate	50%	47%
Disease control at 105 days	65%	61%
Primary progression	12%	19%

Table 2
Toxicity of cemiplimab in the initial trials [32,34,35].

	Any grade	High-grade (severe or life threatening)
Diarrhoea	27%	1.7%
Nausea	17%	0%
Fatigue	24%	1.7%
Constipation	15%	
Rash	15%	
Immune related adverse events		10–14%

given intravenously every two weeks. Therapy was continued whilst patients were benefitting and without major toxicity for a maximum of 48 weeks in the phase I group and 96 weeks in the phase II study. There were 26 patients from the Phase I trial expansion cohort and 59 metastatic patients from the Phase II trial. If these numbers appear modest, it is noteworthy that this experience is about equivalent to the entire published literature of cisplatin in CuSCC [33]. The patients mostly had head and neck primary sites and they had been extensively pre-treated (see Table 1). Notably the trial population was reasonably reflective of the real world with a median age in the 70 s. This is relatively uncommon: most trial populations are substantially younger than real world populations. There were substantial response rates (see Table 1); 12% were not evaluable for response. Complete responses were only observed in the metastatic group and occurred in 4 of 59 patients (7%). Toxicity was much as has been experienced with other agents in this class and is outlined in Table 2. Four patients (7%) discontinued treatment because of an adverse event.

Updated results were presented in abstract form in 2019 [34,35], which separated the locally advanced and metastatic groups. For the metastatic group [34] central radiology review confirms substantial responses: of 59 patients there are 10 complete and 19 partial responses (overall 49%). Of great interest is the durability of response: this has been a hallmark of CPI immunotherapy–when patients respond they tend to have prolonged responses. This appears to be the case here: 63% of responses lasted over 16 weeks and 75% of responders had a response of greater than 1 year. In other malignancies responses to CPI immunotherapy can be slow, but in this disease the median time to response was 1.9 months—essentially the time of the first scan. The median progression free survival was 18.4 months and median overall survival for the group had not been reached; however follow-up is still relatively short with a median follow-up of just over 16 months. The drug was reasonably tolerated (see Table 2 for details). About 14% had a high-grade immune related adverse event, including 3 cases of pneumonitis: this is typical of the rate seen with single agent PD-1 agents.

There were 78 patients in the locally advanced incurable group

[35]. Central review reported 10 complete and 24 partial responses with a durable disease control rate of 62.8%. The time to response was 1.9 months. Follow-up is shorter with 9.3 months median follow-up. As such the median duration of response, median progression free survival and median overall survivals had not been reached. Overall and high-grade side effects were similar to those in the metastatic cohort with about 10% having a serious or life threatening immune related side effect.

There are no universal predictors of response to CPI immunotherapy. PD-L1 expression has been useful in some malignancies, but was not shown to predict response in these trials. Other potential biomarkers including tumour mutation burden are being analysed but not yet reported.

Alternative Cemiplimab dosing and frequency schedules have been explored with subsequent cohorts treated with 350 mg 3 weekly, and 600 mg 4 weekly. A subcutaneous formulation has also been developed and is being tested. The approved dose in the USA and Europe is 350 mg three weekly.

Cemiplimab is not the only drug in this space: there are a plethora of agents targeting PD-1/PD-L1 of which pembrolizumab and nivolumab are approved for multiple other indications such as melanoma, non-small cell lung cancer, urothelial cancer, tumours with mismatch repair defects (microsatellite instability) and Hodgkin lymphoma. Keynote 629 (NCT02964559) is a Phase 2 study of Pembrolizumab given at 200 mg every three weeks in patients with unresectable or metastatic cuSCC (including patients having prior chemotherapy). This trial has completed accrual and final results are awaited; a preliminary report describes results of the first 10 patients of whom 7 were evaluable [36]. One complete response, 3 partial responses, 1 stable disease and 2 patients with progressive disease were seen. Two patients had high grade immune related toxicity (hepatitis and pneumonitis). A French trial using pembrolizumab in the same schedule (NCT02883556) in unresectable CuSCC with no prior systemic therapy was also reported at the 2019 ASCO meeting [37]. Of 39 patients by 15 weeks there were 2 complete and 13 partial responses for an overall response rate of 38.5%. Treatment related adverse events were seen in 67% of patients and were severe in 8% including liver toxicity and colitis. PD-L1 was positive in $\geq$1% of tumour cells in 77% of patients and did not predict response.

These reports all focus on the clinical trial population who are frequently different from those in the clinic. Park et al. [38] reported on a single institution series of cuSCC patients treated with immunotherapy, including some who were not trial eligible (many trials exclude concurrent chronic lymphocytic leukaemia (CLL) or indolent Non-Hodgkin Lymphoma (NHL)). Thirteen patients were treated, 8 with pembrolizumab and 5 with nivolumab. Three patients had CLL or lymphoma, 2 had xeroderma pigmentosum and 2 had cuSCC arising in a Marjolin's ulcer. Two patients achieved a complete response, 5 a partial response, 4 stable disease and 2 had progressive disease. There was however one fatality from myocarditis.

Assessment of response to CPI is different from most clinician's experience with direct tumour damaging agents such as chemotherapy and radiotherapy. Responses can be rapid (within weeks) but may sometimes take time to evolve and can be complicated by the phenomenon of pseudo-progression, where lesions may enlarge initially or new lesions may appear before an overall reduction in tumour size is seen (see Beer et al. [39] for an introduction to this topic). These responses are thought to be due to an initial inflammatory response with immune cell infiltration into the site of tumour deposits. Some patients can have residual lesions that do not progress over time and remain stable even after ceasing CPI therapy. FDG-PET scanning may have a role in helping to guide management in these situations as has been seen in melanoma (see Aide et al. [40] for a review).

Special populations

Patients with advanced cuSCC who are also solid organ transplant recipients; have intercurrent autoimmune disease or a haematological malignancy require special consideration in relation to CPI therapy. As discussed above immune suppression associated with solid organ transplants is a potent risk factor for the development of cuSCC; cuSCC are often multiple and follow an aggressive clinical course, representing a significant cause of mortality for these patients [25]. PD-1 signalling is believed to be an important component of organ rejection and there is a theoretical consideration that anti-CTLA4 antibodies may be less likely to induce graft rejection.

Outcomes of CPI treatment in these patients can potentially be no response of the tumour and rejection of the graft, highlighting this high-risk situation. Despite this there are case reports and series of organ transplant patients both with cuSCC and other malignancies being treated with anti-PD-1 antibodies and achieving clinically useful responses and maintaining their graft. A large US cancer centre recently reported their experience with 39 patients treated with CPI therapy [41]. 40% had rejection of the graft, which generally occurred quickly (median time to rejection was 3 weeks) and about a third of patients had to stop therapy because of graft rejection. Just under half of the patients with graft rejection died. About one third of the patients with melanoma had responses to therapy.

Formal trials are being conducted in this area. An Australian trial (ACTRN12617000741381) is evaluating nivolumab in renal transplant recipients with incurable malignancy of a type frequently responsive to CPI therapy such as CuSCC. A US trial (NCT03816332) is examining use of tacrolimus and prednisolone immunosuppression with nivolumab and ipilimumab in a similar patient population. These data, and those from other planned trials, will be invaluable in enabling estimating of the true rates of both response and rejection after CPI therapy. Renal transplant patients have been chosen as the study population given the potential to salvage rejection with a return to dialysis. Intensive biomarker assessment will also be critical to help better understand the biology and nuances of immunological manipulation in transplant patients; the Australian trial excludes patients who have high-titre HLA antibodies, as investigators believe this is a biomarker for risk of graft failure (PT Coates personal communication).

Patients with haematological malignancies, particularly Chronic Lymphocytic Leukaemia, are predisposed to cuSCC, often with aggressive features or clinical course [42,43]. This is a particular issue for white populations in lower latitudes such as in Australia and southern US. Such patients were excluded from the Cemiplimab registration trial and Keynote 629. It will be important to study these patients prospectively to ascertain response rates and toxicity, as well as gleaning any impact on the underlying haematological condition. Initial data from a case-control study of patients with melanoma and CLL suggest that response rates and outcomes were similar [44], and CPI therapy is being explored in the treatment of CLL in combination with other agents (NCT02420912).

Patients with co-existing autoimmune disease requiring immune suppression are excluded from most CPI clinical trials and the Cemiplimab and Keynote 629 studies were no exception. Survey series from patients treated off-trial with CPI and a background of autoimmune disease suggest that many patients can be treated, however careful supervision is required as there is a significant risk of flare in the pre-existing condition (rates of toxicity requiring immunosuppression are about 2–3 fold higher than the general) and there is also a significant incidence of other high grade autoimmune toxicities [45]. Clinicians need to carefully weigh the risks of exacerbating or causing relapse of an autoimmune disease against the threat posed by the patient's cuSCC and whether other alternatives are available. Patients and clinicians may have greater tolerance for a flare in an autoimmune arthritis than for instance an autoimmune neuropathy and hence treatment decisions need to be carefully individualised.

The role of CPI in the rare patients with a strong genetic predisposition to cuSCC, such as xeroderma pigmentosum, is unclear. The extremely high tumour mutational burden in XP suggests CPI therapy could be useful and there are isolated case reports confirming activity [46]. Clinical observation of patients treated for other malignancies suggests that CPI use can sometimes be associated with resolution or improvement in actinic skin changes or early malignancies however new cuSCC do occur in some patients whose metastatic disease is responding to CPI.

Future

Two adjuvant placebo controlled randomized controlled trials of immunotherapy in high risk resected cuSCC are currently recruiting globally. Keynote 630 (NCT03833167) is using pembrolizumab and REGN1280-Onc-1788 (NCT03969004) cemiplimab. Both of these trials mandate adjuvant radiotherapy following surgery. This is common practice in Australia and the US based on outcomes from historical series, although for which there is no strong prospective, randomised trial evidence. Both of these trials are notable also for permitting cross-over and re-treatment. Importantly, the absolute recurrence risk in the cohorts entered on these trials will need to be sufficiently high to detect a clinically useful effect from the addition of CPI.

The other currently targetable checkpoint is CTLA-4. CTLA-4 antibodies have not been formally tested as single agents, but there are case reports of efficacy [47]. Combination of anti-CTLA4 targeting antibodies with anti-PD-1 agents [48] have shown improved activity in melanoma and renal cell carcinoma, although at the cost of significantly more toxicity (especially colitis, hypophysitis and diabetes) [49] which is likely to be particularly germane to the (generally older) cuSCC population. Alternative doses and schedules of anti-CTLA4 administration have been used in other settings with a better toxicity profile [50]. This is a strategy likely to be tested in advanced cuSCC. There is a multitude of inhibitors of other checkpoints being explored [51]. Should there be demonstrable efficacy it would be logical to extend this to CuSCC.

Oncolytic viruses are genetically modified viruses that are usually given by direct intra-tumoral injection with the intention of causing both direct tumor necrosis, and by release of antigens in the context of a strong immunogenic stimulus triggering a significant host immune effect with generalized activity [52]. This strategy is also being used in combination with CPI blockade hoping that the CPI therapy will enhance the effect [53]. There is a recruiting study examining such a strategy in CuSCC using Cemiplimab with the oncolytic virus RP1 (NCT04050436). A key issue for this trial will be whether the response generated is sufficiently superior to that achieved with Cemiplimab alone to warrant the logistic demands of direct tumour injection. It is possible that this approach may become a strategy for disease resistant to anti-PD-1 CPI alone.

Interleukin-2 (IL-2) is a cytokine with anti-tumour activity, first demonstrated over 20 years ago [54]. High-dose intravenous therapy resulting in responses in 5–27%, but responses could last decades [55]. Use was limited by significant toxicity; some regimens required intensive care support to deliver [56]. More recently developed modifications of IL-2 [57] appear to exert therapeutic effect with less toxicity and are currently being tested in clinical trials in other cancers and cuSCC patients would be a logical setting, but always bearing in mind that more aggressive therapy may not be tolerated by the typical patient with CuSCC.

Conclusion

The treatment of patients with unresectable, locally advanced or metastatic cuSCC has been revolutionised by the demonstrated clinical effectiveness of CPI. CPI therapy has delivered a significant rate of tumour response and importantly durable responses that can continue beyond cessation of treatment. These responses have occurred with generally manageable toxicity.

Nonetheless, important questions remain. Firstly, is the issue of age and frailty: the majority of patients with this disease are older, and many will be frail. Although all trials involve selected patients, the high median age of participants gives some reassurance this will translate outside of the trial setting. Immunotherapy in the fitter older patient does seem to have similar activity and toxicity as in younger patients [58]. Secondly, there are significant issues with special populations. The safety and effectiveness need to be studied in patients with autoimmune conditions and underlying or previously treated haematological conditions, important populations experiencing advanced cuSCC who were not included in trials. Patients with solid organ transplants are another group who may develop difficult to treat cuSCC and for whom CPI may pose unacceptable risks. Thirdly, not all patients will respond and some will respond and then progress. The biology of this is an area of obvious and substantive interest, as is the predicament of what further therapy might be active. Combinations of CPI with other agents including additional immunotherapeutics, radiotherapy or chemotherapy are all potentially worth study to try and maximize responses or reduce late failures. Longer follow-up of trials, and real world data collection is required to ascertain the rate of acquired resistance, and relapse. As an extension of this point, many current CPI trials now stipulate maximum treatment durations (typically 2 years). The outcome of patients who relapse after completion and their response to subsequent therapy will be of considerable importance. Finally, having now found therapies that are highly active and can be tolerated in the palliative treatment of CuSCC we need to see whether these treatments can be used in curative treatment. Current trials are exploring the use of Cemiplimab and Pembrolizumab as adjuvant treatment for high risk resected patients. There is interest in their use as neo-adjuvant agents i.e. preceding definitive radiotherapy or surgery for locally advanced disease, to reduce the morbidity of resection and perhaps also to reduce the risk of recurrence.

CPI therapy is a major advance in the systemic treatment of advanced cuSCC and important clinical trial data will be forthcoming over the next few years to guide optimal use of these agents.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.104459.

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